II. Perinatal HIV Transmission and Antenatal/Intrapartum Interventions

Extent of Perinatal HIV Risk in the Developing World

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The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that approximately 600,000 infants acquire HIV from their mothers each year. Those figures correspond to about 1,600 children each day. Of those, about two-thirds are in sub-Saharan Africa, about 30 percent are in South and Southeast Asia, and about 2 percent are in Latin America and the Caribbean. In other words, the great majority of mother-to-child transmission is occurring in developing countries.

Estimates of the risk. We are fortunate that one of the principal methods of conducting surveillance on the HIV pandemic has been serologic surveys in antenatal women. There are many reasons for that: access to populations of interest, relative simplicity, and consistency of methodology from place to place. While antenatal women were selected to be as representative as possible of the general population, we know that they somewhat under-represent the HIV levels in older women, and somewhat over-represent HIV levels in younger women, because of the biases in terms of who becomes pregnant.

Nonetheless, these surveys provide a direct indication of the risk of HIV transmission from mother to child. And there are fairly extensive data available, probably the most available of any real data on the HIV pandemic.

All data on the level of HIV infection in childbearing women that have been published, either in journal format or in conference abstracts or in health department publications and so forth, have been collated by the U.S. Department of Census into a large database. The database was developed in collaboration with the U.S. Agency for International Development (USAID) and working closely with UNAIDS, so the data are available in many formats.[1] What I will be showing you is a summary from this database, which was prepared in collaboration with UNAIDS. Thus, the maps show the actual levels of infection among women having babies, at least in the particular clinics surveyed.

As will be discussed subsequently in this workshop, the actual transmission risk is somewhat variable, since different factors affect it. One key time of transmission occurs

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[1]This database is available through both UNAIDS and International Programs Center, U.S. Bureau of the Census, Washington, D.C. 20233-8860 (e-mail: kstaneck@census.gov).

before and during birth; the other is the very problematic transmission that occurs after delivery, primarily through breast milk.

I do not know if one of the subsequent speakers will cover the topic of HIV-2 versus HIV-1, but I would point out that, from the information available, HIV-2 is much less transmissible from mother to child, as indeed it is less transmissible heterosexually than HIV-1. For example, in a study in Côte d'Ivoire, HIV-1 had a 25 percent transmission rate and HIV-2, only 1 percent. Our comments in this workshop will focus primarily on HIV-1. Although, presumably, there is no contraindication to trying to prevent HIV-2 transmission from mother to child, there is little of such transmission, even in the places where HIV-2 infection is common.

Because we are in North America, we will start with Mexico, where there a prevalence of somewhat less than 1 percent, but a finite rate. Thus, in Mexico, as in the other two countries of North America, the infection level overall is modest compared with some other parts of the world.

Nonetheless, in certain subpopulations within any of these countries, HIV transmission from mother to child remains an important risk. And obviously for an individual woman who is infected, the risk of transmission to her baby is essentially the same as in other parts of the world.

In Central America, we find some zones reaching to a little more than 1 percent prevalence. Honduras has, to some extent, the most information available for Central America, but also apparently the highest proportions of infected women, at least in several areas of the country.

Moving down into South America, we find only one region in northwestern Brazil and Guyana with prevalence greater than 1 percent. The highest level is found in Brazil, with more than 5 percent, making it the most affected country in the continental Americas. In other parts of South America, although present, HIV still occurs at modest rates (generally less than 1 percent) compared with some other parts of the world.

In the Caribbean, the HIV prevalence levels in some areas exceed 1 percent, but generally remain less than 5 percent. Rates are higher in Haiti–more than 5 percent–and at a modest level in the Dominican Republic, on the other end of the island.

To the east, the Indian subcontinent has had significant levels, up to nearly 5 percent in Mumbai (formerly known as Bombay) and several other parts of India. While the levels of infection are generally low compared with those in some parts of Africa (which we will show later), because of the huge populations in India and in the region, even modest levels of HIV among women become an extremely important perinatal transmission problem.

Further east, in Southeast Asia, at least one area in Myanmar has more than 5 percent prevalence among pregnant women; however, appreciable levels between 1 and 5 percent are found in Cambodia and other parts of Myanmar. Lower levels of infection are seen in Vietnam and in Malaysia.

Thailand has one of the most extensive collections of data from serosurveillance, a

really admirable program which started early enough to actually detect the increases in HIV over time. Several parts of the country, particularly in the far north, have a prevalence of more than 5 percent among pregnant women. But HIV is detectably present, a few percent generally, in most other parts of the country as well.

For the islands of Oceania, extensive data are not currently available. The rates that have been observed are relatively modest (well under 1 percent) compared with other parts of the world.

North Africa certainly has HIV present, but it has not reached the high levels seen in other parts of the continent. Sudan has some rates that, while still under 5 percent, exceed the 1 percent level.

In West Africa, we start to see higher HIV levels, mostly ranging from 5 to just less than 10 percent, with a few areas with greater than 10 percent. In other words, 1 or more of every 10 women coming to antenatal clinics in several West African cities are infected. So, clearly, very important levels of HIV infection are found among pregnant women in the region. The highest levels in this region have been found in Côte d'Ivoire and Burkina Faso.

In Central Africa there are several areas in which the levels of infection exceed 10 percent, particularly in the Central African Republic, although 5-10 percent is the more typical range.

Moving to East Africa, we see the first of the 20-plus percent levels. In urban areas of Kenya and Uganda and in several places in Rwanda and Burundi, the prevalence is 20 percent or more. That is to say more than one of every five women who are giving birth is infected. So, obviously, there are very serious problem areas even outside the major cities.

The Horn of Africa also has significant levels of infection among women, particularly in Ethiopia, which has rates of 20 percent and more.

Southern Africa appears to have the highest HIV prevalence levels in the world, at least at this time. Prevalences of greater than 20 percent among women having babies are common in a number of countries. Prevalences of more than 30 percent are seen in Botswana, Lesotho, Malawi, Zambia, and Zimbabwe. And, as some of our South African colleagues here at the meeting can testify, prevalences in some areas are still increasing rapidly.

This is a quick overview of data from the developing world indicating the extensive problem levels of HIV among women having babies. Even in the countries that at this point appear to have lower levels, some subpopulations and certainly some delivery services have been severely affected, creating a need for intervention now that there is an opportunity.

The opportunity. Previously only the long-course regimen of AZT, the 'O76' treatment, had been shown effective, with a 65 to 75 percent reduction in transmission. However, for most developing countries, this intervention could not be implemented because of cost and logistical complexity. We would also point out that the international

community did not support trying to make this approach available for these very reasons. We are hopeful that now, with a lower-cost, less complex intervention approach, the international community will provide some of the assistance needed to be able to deliver interventions in countries with limited resources. This workshop is part of that process.

This workshop will cover the Bangkok study in some detail and summarize the various other intervention approaches that remain under evaluation. Hopefully, there will be data available on those other approaches later in this calendar year.

A challenge. A significant new challenge lies ahead, in addition to the costs of even the short-course regimen of AZT, the problems of implementation, and the troublesome issue of breast-feeding. This new challenge is the demand for treatment. As antiretrovirals are made more available in a number of societies, partly through the intervention of UNAIDS and partly from the demands of affected communities for treatment, the question is raised of how can you just treat the woman for 4 weeks with AZT (if that is the intervention being used) and then stop. Are there not obligations to the mother after delivery? What about her HIV infection and her health? This is a very important question. But we must also recognize its implications. If, as part of a perinatal intervention program, the mother is ensured treatment for the rest of her life, then the costs even for the first month of the woman's therapy would exceed the cost of the intervention to prevent the transmission of HIV from her to her child. And very quickly the costs of preventing mother-to-child HIV transmission becomes prohibitive for most developing countries. Those are exactly the places for which the low-cost interventions were sought.

I do not have an answer. But clearly this is an issue which is going to take on enormous political and, to some extent, ethical debate. Almost certainly there will be people getting up at microphones [at the International AIDS Conference] in Geneva and denouncing people for forgetting about the woman in perinatal interventions. But just remember, if we link treatment to prevention of mother-to-child transmission, it means that because of cost it may not be possible to do the mother-to-child transmission prevention where it is most needed. I think this issue remains a challenge for which we will not find many answers at this workshop, but it is a background issue of major importance.

Mother-to-Infant HIV Transmission: Modes, Timing, Mechanisms, and Risk Factors

Presented by Maryglenn Fowler, M.D., M.P.H.
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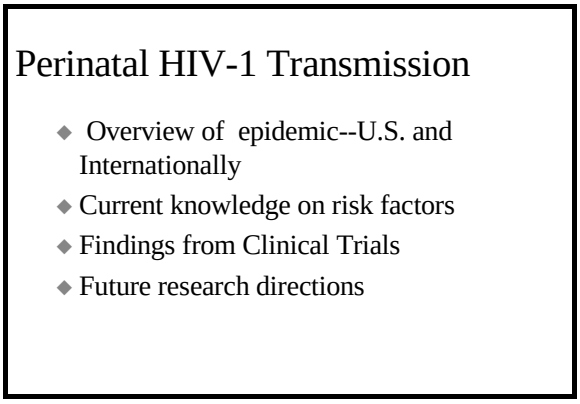
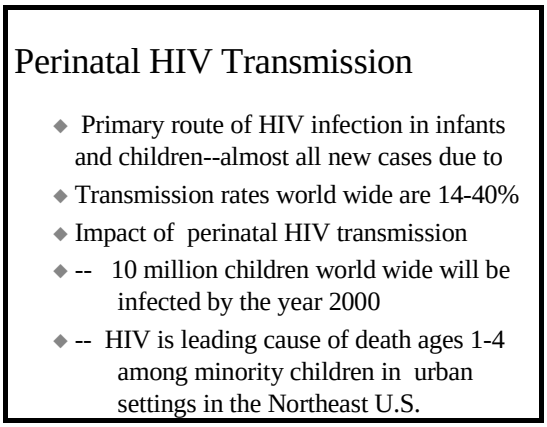


I would like to give a brief overview of the risk factors for transmission of HIV and also to discuss briefly our future research needs. Since the CDC Thailand short-course AZT results were announced, CDC, UNAIDS, and other research partners, including NIH, have been focusing on implementation approaches.

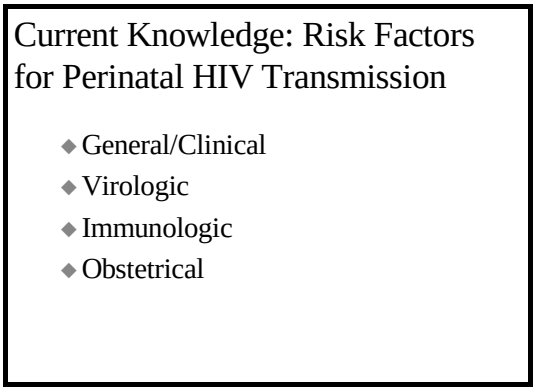
Dr. Dondero already has shown you that this is still a major pandemic, despite the successes that we are seeing. Currently it is estimated that more than 30 million individuals are infected with HIV. Most infected persons at this point are in Africa, but also we are seeing major explosions of the epidemic in the Far East.



Regarding children who are HIV infected, the current estimates are about 1.1 million children living with HIV and as many as 1,600 new HIV infections occurring in infants each day from mother-to-infant transmission around the time of labor and delivery or through breast-feeding.

To highlight where the epidemic is going, I know we are all very aware of the current epidemic in Sahara and Africa. But, in particular, a major focus of the epidemic is emerging in the Far East, particularly in Cambodia, Thailand, and India.

In terms of the ACTG O76 results, which demonstrated the efficacy of an intensive regimen of AZT given to the mother prenatally and during labor, as well as to the infant, I believe it is important to look at transmission rates prior to the ACTG 076 results. These transmission rates give a sense, particularly with the African studies, of the very high rates compared with the rates that were seen in Europe and even in the United States prior to the ACTG O76 trial. And the contrasts now are even greater. Anecdotally, in the United States we are seeing rates between 2 and 5 percent. In Europe the rates are also very low. So the implementation of a deliverable antiretroviral regimen is a crucial issue for most of the developing world.



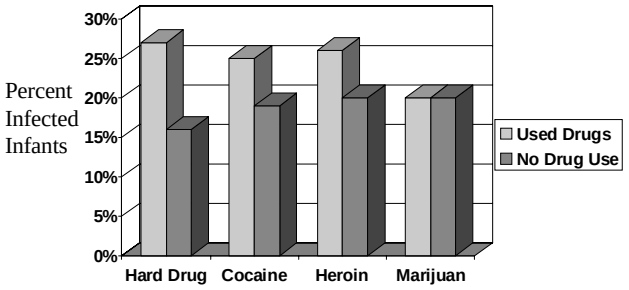
What I wanted to do first is discuss what we know about risk factors for mother-to-child HIV transmission. There has been much progress in terms of understanding overall virologic and immunologic, as well as obstetrical, risk factors. One of the issues that is particularly important is understanding which of these risk factors are still important in the presence of antiretroviral interventions. Already it appears that a number of the risk factors may get washed out in the face of the AZT treatments. This situation will need to be looked at carefully as these risk factors may change over time. To date we do not have information that can completely delineate changes in the importance of certain risk factors.

Clinical Maternal Risk Factors for Perinatal HIV Transmission

- Increased Illness Severity
- Maternal Drug Use
- Low Vitamin A levels--International
- Preterm delivery <34 weeks
- Nonreceipt of 076 zidovudine regimen
- Breastfeeding
- Unrelated to maternal age, race/ethnicity, or previously infected child

The clinical risk factors for perinatal HIV transmission have been fairly well described. These include increased illness severity in the woman; the mother's drug use during pregnancy; low vitamin A levels, which is particularly important in developing countries; pre-term delivery; nonreceipt of the ACTG O76 AZT regimen, which is the most crucial means right now for reducing the risk of transmission; and breast-feeding. In contrast, perinatal HIV transmission has not been related to some of the usual demographic factors, such as maternal age, race/ethnicity, or history of having a previously infected child.

Maternal Prenatal Drug Use and Infant HIV Infection Status--WITS



Rodriguez , AIDS 1996

I wanted to present some of the data from one of the U.S. studies, the Women and Infant's Transmission Study (WITS), again pre-O76, which looked at risk factors for transmission. One of the factors that played out in that population, where about 40 percent of the women were drug users, was that drug use, such as with cocaine and heroin, increased risk for HIV transmission. However, the mother's drug use is more important in the developed world and much less so in developing countries.

In the developing world, low vitamin A levels in the mother have been correlated with increased rates of infant HIV infection. There are several clinical studies that hopefully this year will have results regarding the role of micronutrient interventions in preventing mother-to-infant HIV transmission. In the United States, the observational data have been somewhat conflicting. WITS has not shown a relationship in a developed setting in the United States, but some other studies have suggested it.

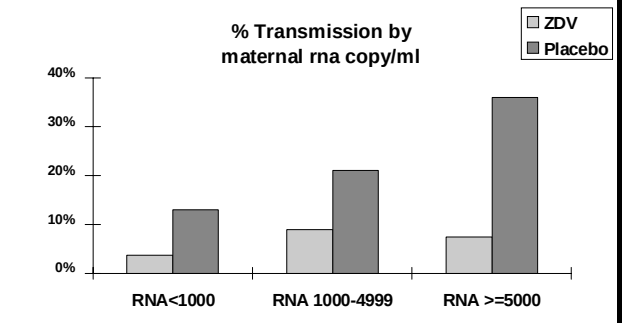
Maternal Viral Load and Risk of HIV Transmission: Results

- All studies to date find a general relation of increased maternal viral load and risk of perinatal HIV transmission
- Most studies (5/7) do not find a threshold below which no transmission occurs
- The 076 zidovudine regimen appears to be protective at all levels of maternal RNA (ACTG 076 findings)

Maternal viral load data have also been very carefully examined in a number of different studies. Most of the studies have shown a very clear relationship between increased viral load in the woman during pregnancy and the risk of transmission.

However, most studies have not shown a threshold below which there is absolutely no risk of transmission. The other important information is that AZT appears to be protective at all levels.

ACTG 076 Transmission Rates by Maternal Entry RNA Levels



Sperling, 1996

This slide presents the data from the O76 trial. As you can see, the purple bar represents the placebo group. There is a very strong trend for increased viral load to be

associated with risk of transmission. When you look at the lighter bars (the ZDV groups), you again see a general association with the increasing viral load, but it is much dampened, so that at all levels of maternal viral load, ZDV appears to be very protective against transmission.

Maternal Immunologic Risk Factors for Perinatal HIV Transmission

- Lower CD4+ counts associated with increased risk of perinatal transmission (ECS 1992, WITS 1996, French 1996)
- Maternal neutralizing antibody -- conflicting studies
- Antibody-Dependent Cellular Cytoxicity unrelated to risk of transmission (Luzuriaga, 1996)

The other area that researchers have looked at in detail relates to maternal immunologic factors and transmission risk. Across all major studies in European and U.S. cohorts, lower CD4 counts have been associated very consistently with an increased risk of transmission. The neutralizing antibody data are conflicting, with some studies showing a protective effect of maternal neutralizing antibody and others not showing a protective effect. Presence of antibody-dependent cellular cytotoxicity appears, although the studies are small, not to be related to a decreased risk of transmission.

One of the areas for which there are some emerging data is related to immunogenetics. Of interest, HLA disparity between mother and infant appears to be protective according to a Kenyan study by Kelly McDonald.

Maternal CD4+ Counts and Risk of Perinatal HIV Transmission

		Percent Infected Infants
◆ ECS	N=258	
CD4	>700	6%
	400-700	22%
	<400	19%
◆ WITS	N=881	
CD4	>500	12%
	200-500	19%
	<200	23%
◆ French	N=963	
CD4	>500	17%
	200-500	28%
	<200	27%

This slide summarizes the immunologic risk factor data from three large studies. The increased risk of perinatal transmission when the mother has a low CD4 count is very consistent. In fact, it is one of the few factors that, following the O76 results, continues to be a consistent risk.

Intrapartum Factors that may Contribute to HIV Transmission

- During Labor
  disruption of placenta
  maternal-fetal blood exchange
  duration of membrane rupture
  chorioamnionitis
- Vaginal Delivery
  HIV in vaginal secretions and blood
  ob procedures --instrumentation,
  internal monitoring
  maternal vaginal STD's--e.g. syphylis
- Infant abrasions, swallowing blood

Information also has been obtained on obstetrical risk factors for transmission. Understanding obstetrical risk factors is very useful because, in planning interventions, one could potentially intervene around the time of delivery.

Obstetrical Factors and Risk of Perinatal HIV Transmission

- Duration of membrane rupture > 4 hours related to doubling of risk of infant HIV infection (3 US studies)
- C-section, in metanalyses associated with 20% reduction in risk of transmission
- French study of 1632 infants found a number of obstetrical factors were related to risk of infant HIV infection
- Chorioamnionitis-- increased risk in Zaire

Duration of membrane rupture of greater than 4 hours has been related in several studies to increased risk of transmission, often with a doubling of risk. Regarding the role of caesarean section, a number of meta-analysis, as well as an ongoing clinical trial in Europe, have been addressing that issue. There is a meta-analysis that will be presented at the Geneva meeting that should provide more information. To date, the data suggest that an elective caesarean section may lower the risk of transmission compared with vaginal delivery.

A large French cohort study by Mandelbrot that was published this past year also suggests a number of other obstetrical risk factors for transmission, including maternal infection with a sexually transmitted disease (STD) during pregnancy and certain obstetrical procedures.

WITS Obstetrical Factors and Risk of Perinatal HIV Transmission

	Infected % (#)		Pvalue
Duration Membrane Rupture in Hours			
0- 4	12%	17/146	<.001
5-12	22%	15/67	
13-24	21%	7/33	
>24	50%	14/28	
Duration of Labor			
0-6	18%	17/95	0.49
7-12	29%	23/80	
13-24	12%	7/60	
>24	17%	3/18	

Landesman NEJM 1992

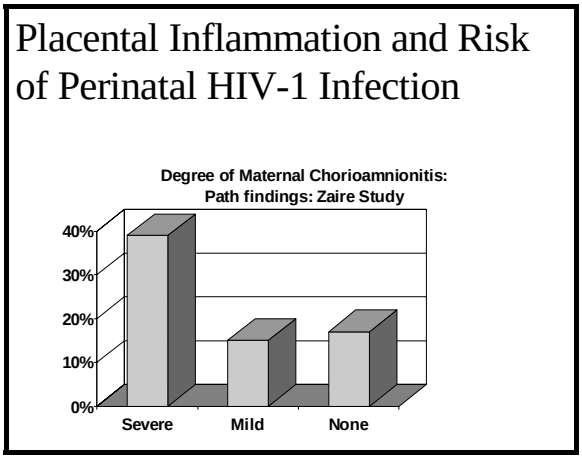
This slide presents data from one of the U.S. studies looking at duration of membrane rupture. WITS data suggest that after 4 hours duration of membrane rupture, the risk increases from less than 10 percent to about 25 percent–again, this was pre-O76 data–and then after about 24 hours increases substantially, up to as much as 50 percent.

French Obstetrical Study
N=1632 Mandelbrot, AmJOB/GYN, 1996

Obstetrical Factors	Rel Risk	P value
Cervicovaginal Infect.	1.3 (1.1-1.7)	0.018
Premature membrane rupture	1.4 (1.1-1.8)	0.009
Preterm Delivery <37 weeks	1.4 (1.1-1.9)	0.02
STD's	1.5 (1.1-2.0)	0.003
Hemorrhage in Labor	1.9 (1.1-3.2)	0.02
Amniocentesis orother needle procedures	1.9 (1.3-2.7)	0.007

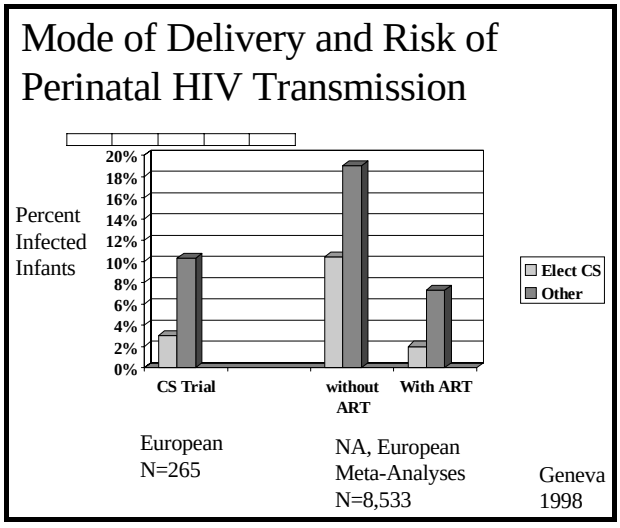
From the Mandelbrot study, some of the risk factors include STD and cervical/vaginal infections as well as pre-term delivery. These risk factors may interact. For

example, if one could reduce STDs related to chorioamnionitis and help prevent pre-term delivery, one might be able to significantly reduce the risk of transmission by affecting several risk factors.



One of the areas in which we really have little understanding regarding transmission mechanisms is the role of chorioamnionitis. This slide presents data from a study in Zaire, which found that severe chorioamnionitis was associated with increased risk of infection in the infant.

There have been some follow-up placental studies that have been looked at in fairly small numbers (at this point) in the United States. One is a study by Popek looking at chorioamnionitis and combining that data with duration of membrane rupture data. In that study, you can see that women who have chorioamnionitis on pathology review of the placenta, as well as duration of membrane rupture greater than 4 hours, had the highest risk for infection of their infants. These data were in the presence of antiretroviral therapy.



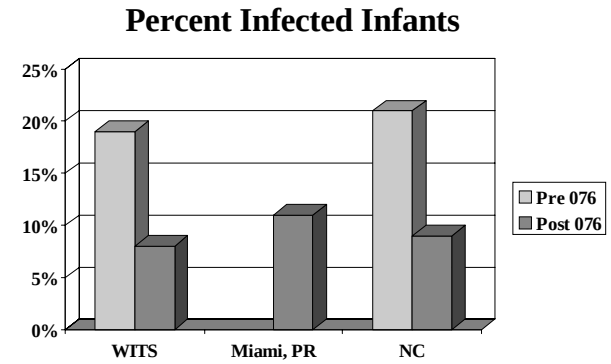
This slide summarizes the various studies that have looked at the caesarean section data. Again, overall, caesarean section delivery does appear to provide a protective effect.

PACTG Perinatal Trial Results

- PACTG 076--AZT prenatally, intrapartum and for 6 weeks to infant resulted in 67% reduction in risk of perinatal transmission (25% placebo group versus 8% AZT group) among asymptomatic HIV infected women
- PACTG 185--AZT regimen in presence of either IVIG or HIVIG resulted in overall transmission risk of 4.8% among more symptomatic HIV infected women

PACTG Clinical Trial Results. This slide summarizes the AZT results from ACTG 076 and ACTG 185. As you are aware, the ACTG O76 trial showed, with ZDV given to the mother prenatally and during labor and to the infant for 6 weeks, a two-thirds reduction occurred in risk of infection, from about 25 percent to about 8 percent. ACTG 185, the next perinatal efficacy trial carried out in the ACTG, looked at whether HIVIC versus IVIG among a sicker group of women lowered the risk of transmission in the presence of AZT. What is particularly intriguing is that, in this group, the overall transmission rate in the background of the O76 regimen was about 4.8 percent. The ACTG 185 data demonstrated that, even among sicker women, AZT is a very important intervention.

Observational Findings Post ACTG 076 Results

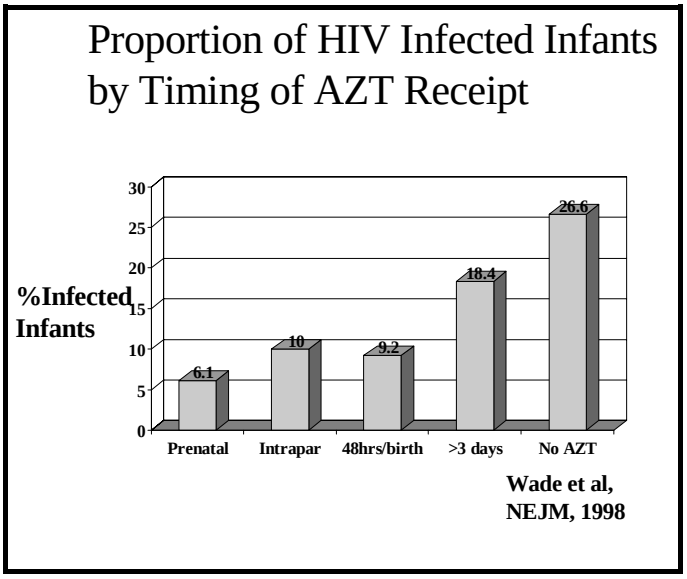


This next slide presents observational data in the United States after the implementation of the O76 AZT regimen.

Timing of Perinatal HIV Transmission

- Evidence supports that transmission can occur *in utero,* intrapartum, and post delivery through breast feeding
- The exact proportion occuring at each time period is not established
- Knowing when most HIV transmission occcurs is key to refining perinatal HIV prevention strategies

Timing of Transmission. Both direct and indirect evidence supports perinatal transmission occurring prenatally during labor and delivery and postnatally.



This next slide presents a study by Birkhead and Wade that was presented in Chicago in 1998; this is for New York City. It again demonstrates the reduced risk for the women and infants who received prenatal and intrapartum AZT. It is a little more detailed about timing of the postpartum doses. These data suggest (albeit, with small numbers) that, for babies who got the postpartum intervention alone but received it within the infant's first 48 hours, there did seem to be some protective effect. However, after 48 hours post-delivery, there appeared to be no protection to the infant in receiving AZT.

Similar findings were reported from a North Carolina study by Susan Fiscus. These

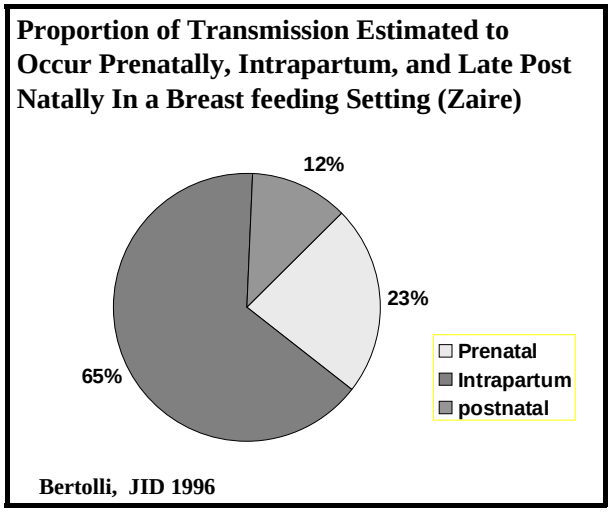
data suggest (although the numbers are small) that if a woman and her newborn received prenatal, intrapartum, and postpartum AZT, the risk for transmission was lowest. If she or her neonate received the prenatal and the intrapartum AZT regimen or the intrapartum AZT regimen alone, again the risk of transmission appears low. In contrast, receipt of postpartum AZT in the infant alone was not very protective. The caveats on this data are that the timing of when the infant received the postpartum dosing is unknown.

These findings lead then to a better understanding of the timing of infection. Transmission can occur during the prenatal period, according to data from products of conception and culture positivity at birth. There are also data from a rural study in the Rakai district of Uganda and a U.S. study suggesting that increased fetal wastage may occur early in pregnancy among HIV-infected women.

Most research indicates, based on timing of the first positive culture, that about two-thirds of the time transmission occurs late in pregnancy and around the time of delivery. An important area for future research will be examining changes in breast-feeding-related transmission if we are successful in preventing transmission around the time of labor and delivery.

To summarize, in non-breast-feeding settings, based on timing of culture positivity, researchers estimate that 25 to 40 percent of transmission occurs prenatally, probably late in the third trimester, and that 60 to 75 percent occurs during labor and delivery.

In breast-feeding settings, transmission rates are higher, as we have seen from the initial transmission rates. Based on data from Bertolli and Ekpini, we believe about 23 percent of infants are positive at birth and are thought to have been infected prenatally. Sixty-five percent of transmissions are associated with intrapartum or early breast-feeding, and 12-14 percent are associated with later postpartum transmission through breast-feeding.



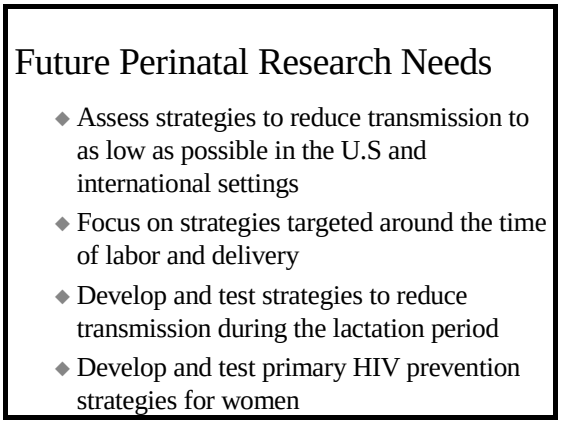
This slide presents data from Zaire that Dr. Bertolli published in 1996 in the *Journal*

of Infectious Diseases. In looking at a breast-feeding setting, you see about two-thirds of the babies are not positive at birth, but become positive in the first several weeks to months of life. This suggests that most transmission probably occurs during labor and delivery, with a smaller proportion, about one-quarter, occurring in utero; 12 percent are late transmission, thought to be associated with breast-feeding.

An update on that at the Ghent meeting in November 1997 suggested a cumulatively increasing rate of transmission postnatally associated with breast-feeding. Overall, an HIV transmission rate of about 3 percent per year related to breast-feeding was reported.

So the overall evidence in terms of timing would suggest that transmission can occur during all time periods. The actual proportion occurring prenatally, intrapartum, or postnatally is probably going to shift with interventions directed at late prenatal and intrapartum transmission. We are already seeing some trend data from the United States, particularly from WITS as well as from California, suggesting a higher proportion of in utero transmission, which may mean that current intervention strategies are impacting more on transmission late in pregnancy and at delivery.

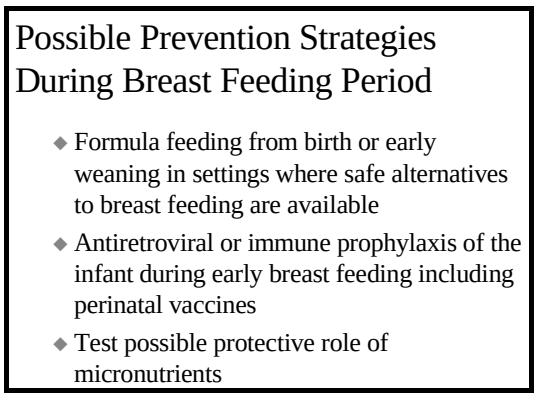
Likewise, in developing country settings with widespread breast-feeding, we are likely to see increased transmission from breast-feeding as we move forward with implementation of peripartum antiretroviral strategies. Focusing on breast-feeding-related transmission will be a key point as we refine intervention strategies.



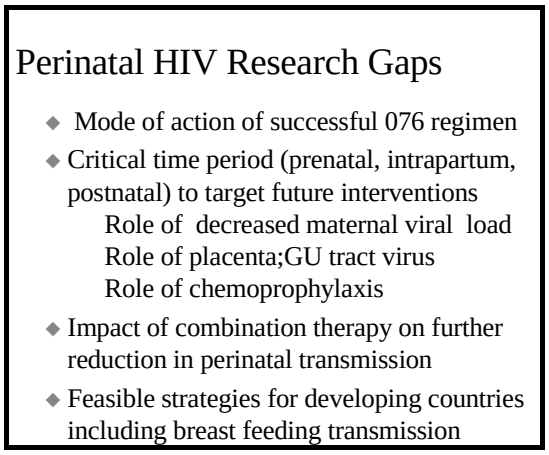
Future research needs. In developed countries, we will continue to try to have an impact on prenatal, intrapartum, and postpartum transmission to strive for elimination of perinatal HIV transmission. In settings where women present right around the time of delivery, the focus needs to be on rapid diagnosis and interventions at labor and delivery.

For settings with breast-feeding, we need to think very innovatively about ways to provide safe formula supplementation and to carefully study strategies that will protect the infant through the breast-feeding period for women who do not have safe water alternatives or who choose to breast-feed after carefully considering the risks.

Obviously, primary prevention of HIV infection among women should be a key goal. Likewise, the implementation of research regarding peripartum antiretrovirals, which is a major focus of this conference, is critically important. Implementation strategies will need to be tailored, depending on the settings, according to what realistically can be done and what will work. In addition, the other area of emphasis should be conducting research to better understand the actual mechanisms of transmission.

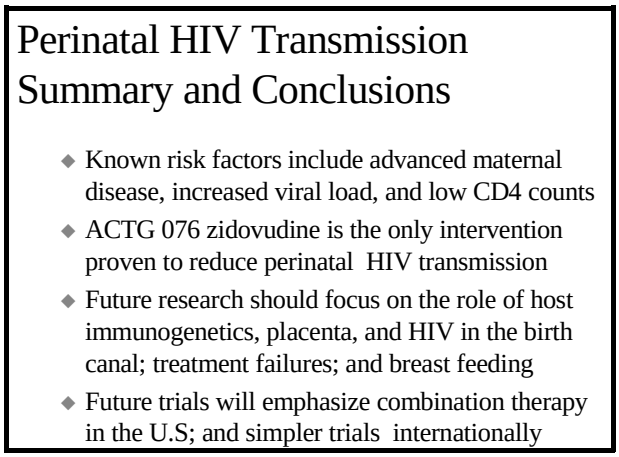


This slide highlights some of the research being planned to address prevention strategies during the breast-feeding period. Some of the approaches include early weaning and perhaps colostrum withholding. Another approach being looked at involves delivery of micronutrients to the infant during the breast-feeding period. Vaccines and passive immune therapy might be another approach to consider to protect the infant during the breast-feeding period.



Research Gaps. We need to be humble as we move ahead. We certainly have had successes, but it is still very clear that we do not understand the infectious unit and what is actually occurring in terms of the mechanism of transmission. The time periods of perinatal transmission appear to be shifting as perinatal interventions around the time of birth are

successfully implemented. We do not know yet the exact impact of the highly effective antiretroviral therapies on transmission rates when given to the women for their own health care. And future research needs to address breast-feeding interventions in many developing world settings.



To summarize, the perinatal use of AZT has significantly reduced perinatal transmission, particularly in the United States and Europe, and now with the CDC Thailand short-course AZT results, it can be implemented in many parts of the world. However, we still do not understand the primary mode of action of the AZT intervention–whether it is related in some degree to viral load reduction or to chemoprophylaxis.

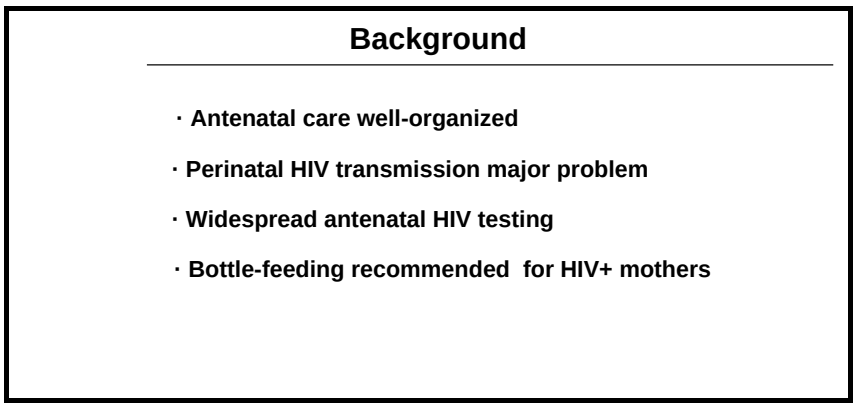
There appear to be some persistent risk factors for transmission post-O76. These include increased maternal viral load, low CD4 counts, and increased illness severity. However, other risk factors are probably going to be much less important in the face of the antiretroviral interventions. At this point, regarding timing of transmission, most transmission appears to occur around the time of birth. But over time, this proportion may shift significantly because of the impact of current interventions.

Future research will need to address, among other critical areas, interventions directed at breast-feeding transmission, as well as better understanding of mechanisms of transmission and modes of action of successful interventions.

Interruption of Mother-to-Infant HIV Transmission: Results of the Bangkok Short-Course AZT Trial

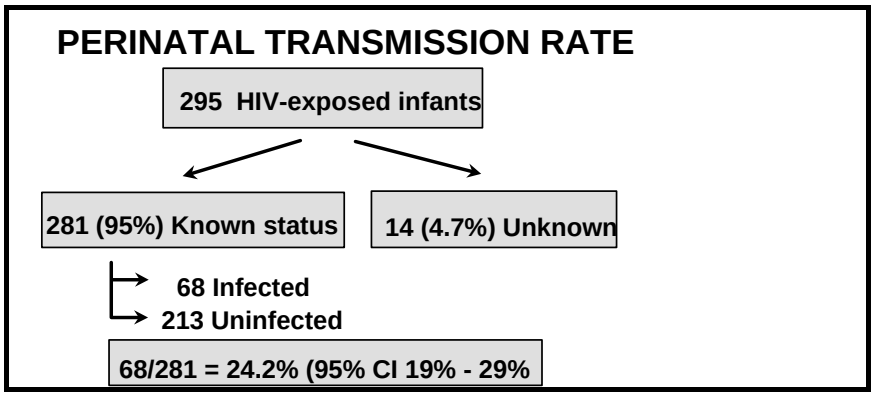
Presented by Nathan Shaffer, M.D.
The HIV/AIDS Collaboration, Bangkok, and CDC

On behalf of our collaborative group in Bangkok, it is a privilege to present the results of our study today. I would like to acknowledge the large group that we have been working with the last 6 years in Bangkok, beginning with our natural history perinatal study and now the AZT intervention study at Siriraj Hospital, Rajavithi, and Children's Hospital, and the Ministry of Public Health. We appreciate the tremendous support from CDC Atlanta and, particularly for the AZT study, from the international network of investigators, as well as the direct involvement of many people in the audience. This truly has been a collaborative effort.



I am going to start by briefly giving a little bit of background on the study, then reviewing some of the key findings of the natural history study, presenting the main data on the AZT study, and suggesting some of the conclusions that will be discussed further at this conference.

As background, in Thailand antenatal care is very well organized and most women deliver in-hospital. Perinatal HIV transmission has been a major problem since about 1991. The antenatal prevalence is about 2 percent nationwide. There is widespread antenatal HIV counseling and testing. (There will be a separate presentation on antenatal HIV counseling and testing later.) In addition, the Ministry of Public Health and the hospitals have been recommending bottle-feeding for HIV-positive mothers and providing support for that for a number of years.



This is a slide from our previous work from 1992 to 1995 to define the background perinatal transmission rate. In a cohort of 281 mother-child pairs with known infection outcome, we estimated an overall perinatal transmission rate of 24.2 percent from the same two study hospitals. The confidence intervals for this point estimate were 19 percent to 29 percent.

Keep in mind that as we are looking at transmission and risk factors in Thailand, we are dealing with HIV-1, subtype E. Questions we had included (1) what are the risk factors for HIV subtype E perinatal transmission, and (2) are there differences or a suggestion of differences between subtype E and subtype B or C that are found elsewhere?

Multiple Logistic Regression Analysis of Risk Factors for HIV-1 Perinatal Transmission

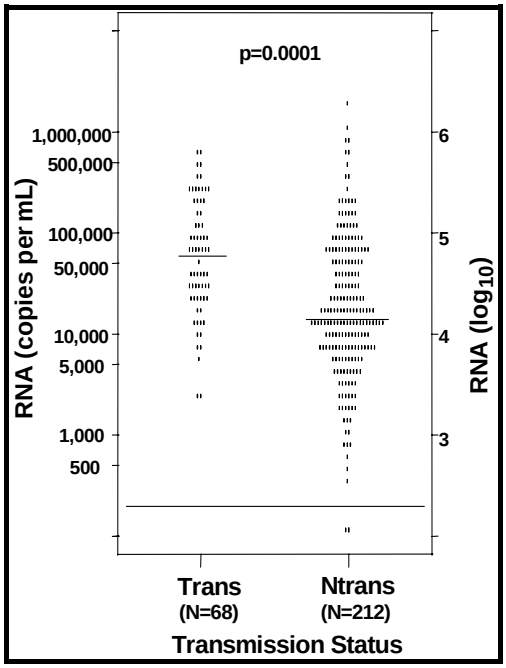
Risk Factor	AOR (95%CI)	P value
Prematurity (<37 wks)	**4.5 (1.1-19.5)**	**0.03**
Vaginal delivery	**2.9 (1.0-10.7)**	**0.047**
NK cell % < median (11%)	**2.4 (1.3-4.6)**	**0.006**
HIV RNA (copies/ml)		**<0.001**
Quintile 2	**4.5 (1.0-31.0)**	
Quintile 3	**10.9 (2.8-72.6)**	
Quintile 4	**11.5 (3.0-75.9)**	
Quintile 5	**24.8 (6.5-163.5)**	

Adjusted for other co-variates in the model

In our multivariate analysis for risk factors, we found that prematurity, vaginal delivery, and viral load were important risk factors. We also found that low NK, or natural killer cells, was an important risk factor for transmission. We have been the only group to report on NK cells.

Overall viral load appeared to be the most important risk factor; our findings on viral load were much stronger than what has been found for several other groups. This is

important because viral load is one factor that an intervention can target. Mode of delivery can also be part of an intervention strategy. Our findings generally are consistent with findings from studies in the United States and Europe. I will show you some of our data on viral load. As I mentioned, our findings were very strong in relation to viral load.



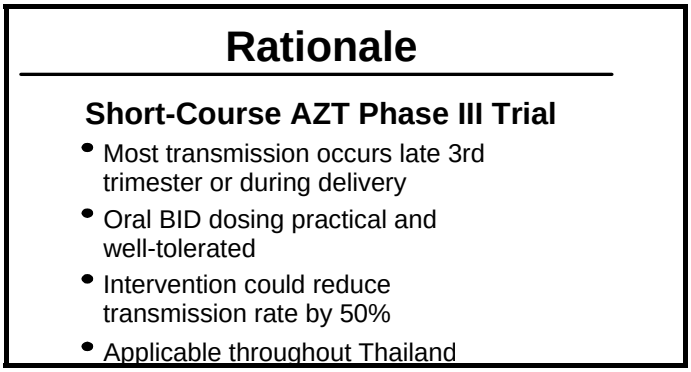
This slide, again, is from our first study, showing the mothers' viral load distribution at the time of delivery, according to transmission status. As you can see, the median viral load level of the transmitters was significantly higher than the median level of the nontransmitters.

Maryglenn Fowler talked earlier about what happens in the lower area, that is, low viral load. It is hard to say that there is an absolute threshold, but our data provide a strong suggestion that the risk of transmission below about 10,000 or 5,000 copies/mL is very low. We used a very sensitive Roche assay that detected a measurable viral load in all but two of the women in our study.

Short-Course AZT - Rationale

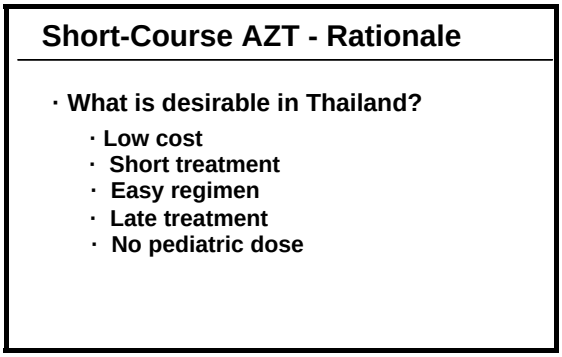
- Full 076 regimen not realistic in Thailand and other developing countries
  - *High cost ($1,000 per teatment)*
  - *Technical difficulty (IV at labor) 5 times/day dosing*
  - *Limited access to women early*
  - *Pediatric dose*

The rationale for the short-course oral AZT study, as you know, is that in Thailand and other developing countries, the full ACTG 076 regimen has not been implemented and may not be realistic because of the high cost and technical difficulty (particularly the intravenous dosing during labor, the five-times-a-day dosing schedule, and the limited access to women very early in terms of second or early third trimester to start the drug). In addition, the 076 regimen poses additional challenges with the 6-week infant dose.

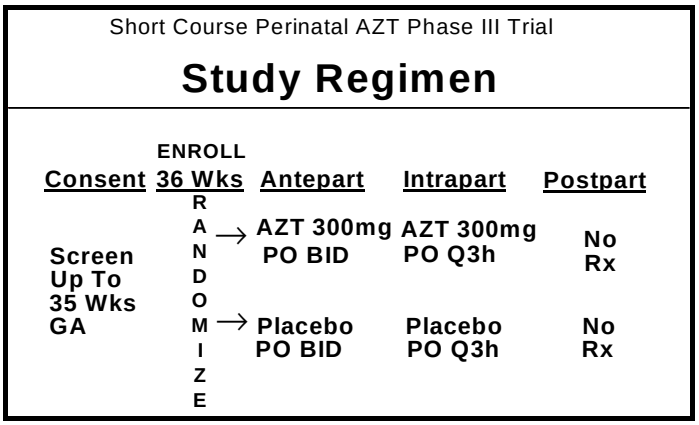


Our regimen was based on indirect epidemiologic evidence from other studies and from our own observations that suggested it would be appropriate to focus on a short course of treatment, with the intervention provided close to the time of delivery. By 1994-95, there was increasing consensus that most transmission seemed to be occurring late in the third trimester or during delivery. We also had some experience in Thailand with adults indicating that an oral BID dosing of 250 mg of ZDV was practical and well tolerated and might be a good alternative to the five-times-a-day dosing used in O76.

Participating in an international network that was designing these trials, we thought that with a short-course regimen it might be possible to achieve an intervention that could reduce transmission by about 50 percent. Our specific goal, working with the Ministry of Public Health of Thailand and with our collaborators, was to demonstrate this, and ultimately show that this type of more practical regimen was applicable and could and would be implemented in Thailand.

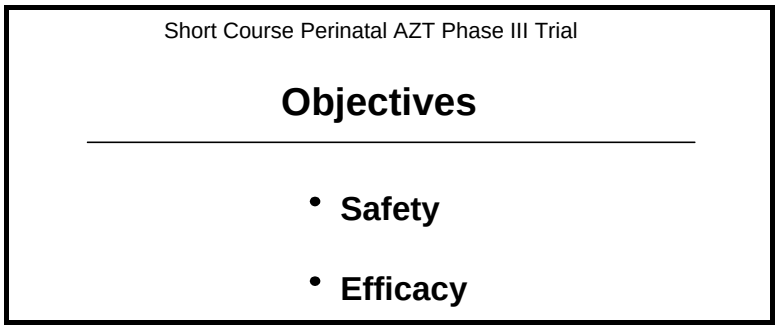


So what we designed had the desirable features of relatively low cost, short duration of treatment, ease in administration and follow-up, treatment starting late in pregnancy (to be able to reach as many women as possible), and no pediatric dose.



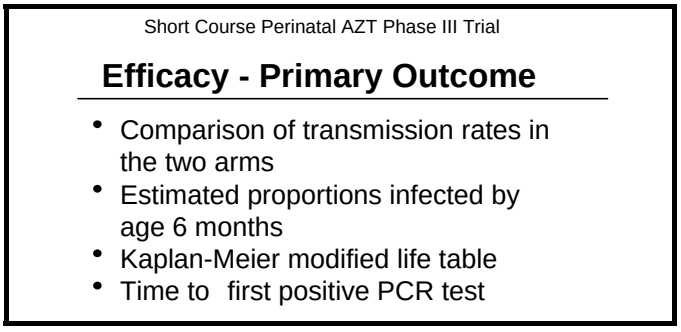
This slide shows the study regimen and the study design that we used. Women were counseled, screened, and informed about our study up to about 32-34 weeks of estimated gestation. Women who consented to the study between 32 and 35 weeks and came back at an estimated 36 weeks gestation were randomized to be part of either the active arm of AZT, 300 mg twice a day, or the identical administration of a placebo.

The regimen was 300 mg twice a day starting at 36 weeks, then one dose at the time of labor, and then one dose every 3 hours until delivery. As part of this regimen, women would be encouraged to come to the hospital as soon as possible after the start of labor. As mentioned, there was no postpartum dose to the woman or the infant, and women were expected not to breast-feed.



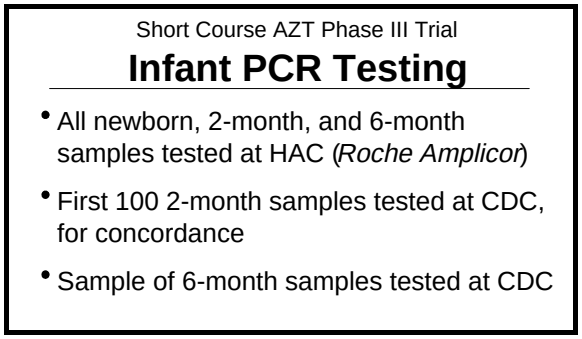
The objectives of the study were to look at both safety and efficacy. I would like to emphasize that while the bottom line was efficacy, we felt it also was important to look at safety. We did have some safety data from O76 at the time, but we were doing a lot of things differently. We were giving a higher dose, a total of 600 mg of ZDV a day in a population where the women were generally smaller than in the United States. We were

also giving an oral dose during labor. As far as we knew, no one had any experience with using an oral dose during labor, either of AZT or other medications, so this really was new territory for us. We also still had a general concern about using drugs in different populations with different genetic backgrounds. So this study was designed to evaluate both the safety and efficacy of the short-course regimen.

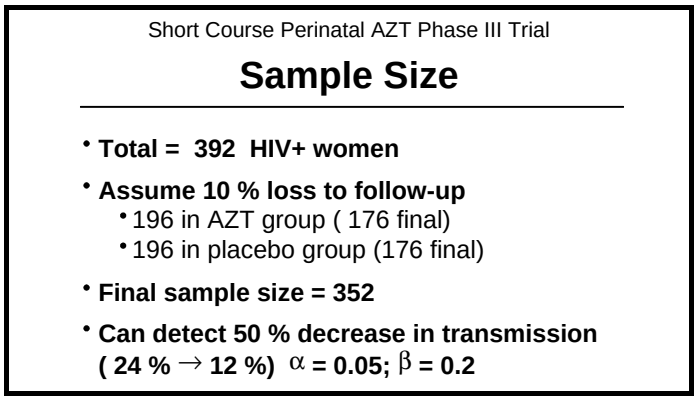


In terms of efficacy, the primary outcome was to compare the transmission rate in the two arms, the active arm and the placebo arm, using the Kaplan-Meier estimate of the proportion of infected children by age 6 months. We chose 6 months thinking that, with DNA PCR testing, we would be sure of the final infection outcome by that age. You will see in the data that we were able to push this forward because our PCR testing could identify infant infection earlier.

For the efficacy analysis, we defined infection, or failure in survival analysis terms, as time to a first positive PCR, using any PCR-positive test result as evidence for infection. Children who had one or more negative PCR results and no positive results were considered uninfected for purposes of the Kaplan-Meier analysis.

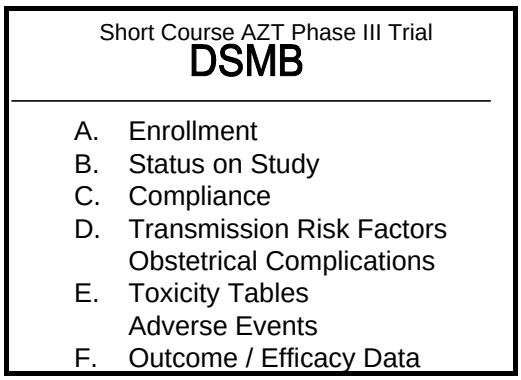


We prospectively tested all venous samples collected at birth, 2 months, and 6 months, and tested them at our HIV/AIDS Collaboration Laboratory in Bangkok using the Roche Amplicor DNA PCR assay. We previously had done some comparability studies with the support of the CDC lab in Atlanta, and we expected very high sensitivity and specificity for this assay.

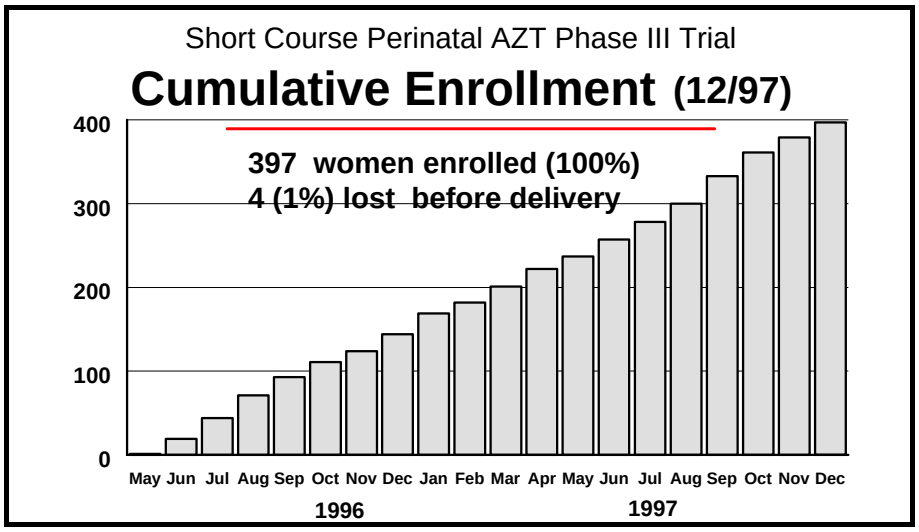


Our sample size for the study called for a total enrollment of about 392 HIV-positive women. We assumed a 10 percent loss to follow-up, so our final sample size target was about 350 mother-child pairs with analyzable outcome data.

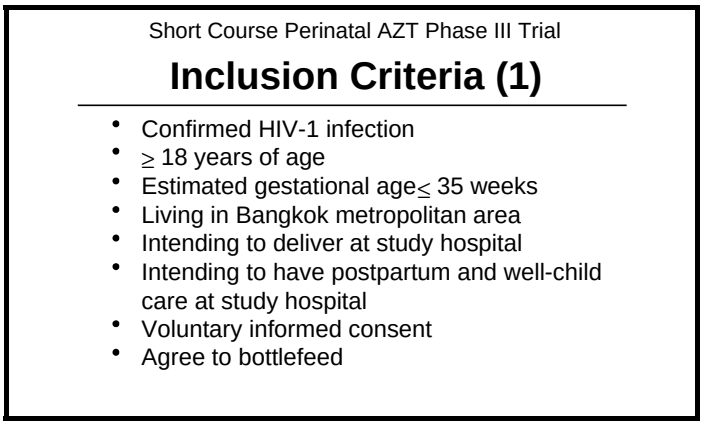
Based on our first study, we used the estimate of a 24 percent background transmission rate. As I explained, we wanted to have enough statistical power to be able to detect a 50 percent decrease in transmission. We chose 50 percent because, first, it allowed us to have a relatively small sample size, but more importantly we felt that this would be a meaningful, implementable regimen only if we could achieve close to a 50 percent reduction. If we had a result that was much below 50 percent, it would be interesting scientifically, but probably would not be an implementable regimen because it would not be effective enough to move public policy in places like Thailand.



Our study was monitored by a U.S. NIH-sponsored Data and Safety Monitoring Board (DSMB), which closely monitored the progress of the study for enrollment, compliance, toxicity, adverse events, and final outcome. We are going to present some of those data in other talks later. There was a Thai representative on the DSMB, a senior Thai official who participated fully in all monitoring activities throughout the study.



We started our enrollment at the end of May 1996. Reaching the full target enrollment took 19 months. Working at our two study hospitals, we enrolled 20 to 25 women per month. Of women enrolled and randomized at 36 weeks, only four were lost to the program before delivery.



Now I will review the inclusion and exclusion criteria, which are very important as we think about moving from a carefully controlled clinical trial to operational research. We need to think about the generalizability and applicability to the general population. Our inclusion criteria were broad in the sense that they included all women who were at least 18 years of age at the estimated time of delivery, were confirmed to have HIV infection, and by history of last menstrual period and clinical exam were less than 35 weeks gestational age.

Our major criteria for participation was actually a geographic one in terms of a stable living situation in the Bangkok metropolitan area, because we were working in a place with

a lot of social mobility, in a very large city with a lot of in- and out-migration. So we selected women based on geographic stability and proximity to the hospital. We also required that the women intended to have their postpartum and well-child care at the study hospitals.

The women were fully informed, signed written consent, and voluntarily agreed to participate in the study. They also agreed to bottle-feed, in accordance with the standard recommendations of the Thai Ministry of Public Health and these hospitals for HIV-positive women.

Short Course AZT Phase III Trial

Reasons for Exclusion (n = 716)

Excluded	N	(%)
Missed ANC appointments	161	(22.5)
Long-term F/U problems	158	(22.1)
Not continue pregnancy	144	(20.1)
Still undecided at 34 W GA	87	(12.2)
GA > 34 wk	71	(9.9)
Age < 18 yr	23	(3.2)
Husband disagrees	9	(1.3)
Placebo concerns	6	(0.8)
Not interested	6	(0.8)
Other	51	(7.1)

May 96 - Dec 97

This slide shows the main reasons why some HIV-positive women were excluded. However, I would like to emphasize that most of these women would be eligible for and accessible to an open AZT program. However, for the clinical trial, with our concern for follow-up and clear outcome, we carefully screened and excluded women who had problems in terms of missing antenatal clinic appointments, who seemed likely to have follow-up problems postpartum (e.g., moving out of town, sending their children somewhere else), or who still were undecided about whether to participate in the study. These were the main reasons for exclusion.

The slide also shows that some women, very few actually, had placebo concerns. The women were fully informed about placebo and understood very well the concept of placebo and a clinical trial. This was not a big issue. Whenever possible, we also tried to inform the husband and obtain his agreement–husband disagreement was a very small factor for not participating.

Short Course Perinatal AZT Phase III Trial

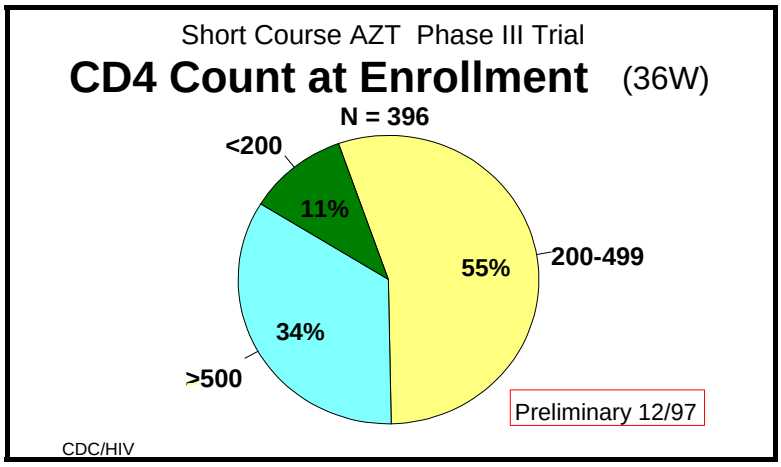
ANC Study Visit Compliance (12/97)

Study Week	Expected	Completed	% Compliance
36 weeks	376	376	100 %
37 weeks	354	352	>99%
38 weeks	307	304	>99%
39 weeks	235	234	>99%
40 weeks	133	132	>99%
41 weeks	56	56	100 %
≥ 42 weeks	38	38	100 %

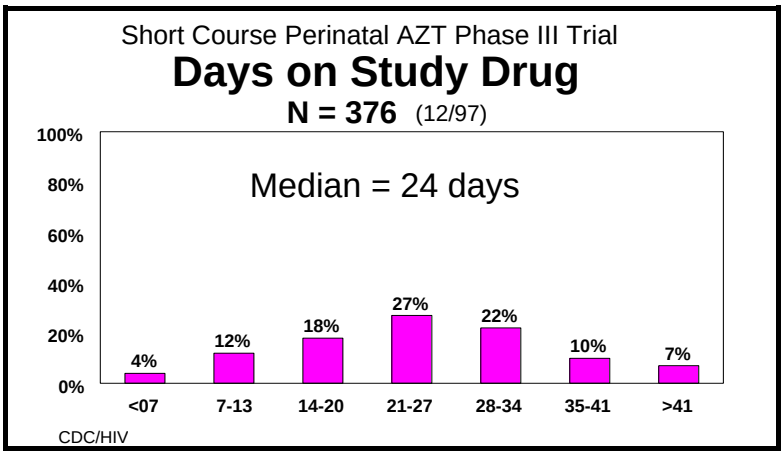
(excludes 4 women who dropped out before delivery)

We will have a separate presentation on compliance. But, briefly, this slide shows that women were randomized at 36 weeks and had study visits every week at the antenatal clinic until the time of delivery. More than 99 percent of the weekly study visits were completed.

I show this slide to emphasize the structure of the study and the hospital and the quality of data in terms of the compliance. This was very reassuring to us–more than 99 percent of the women came to every single weekly visit on schedule and actually within 1 or 2 days of the scheduled visit. We gave out weekly drug doses, weekly packets of the medicine, with an extra 3 days of the study drug; at each weekly visit we did a pill count and review of drug instructions and then gave new drug for the next week.

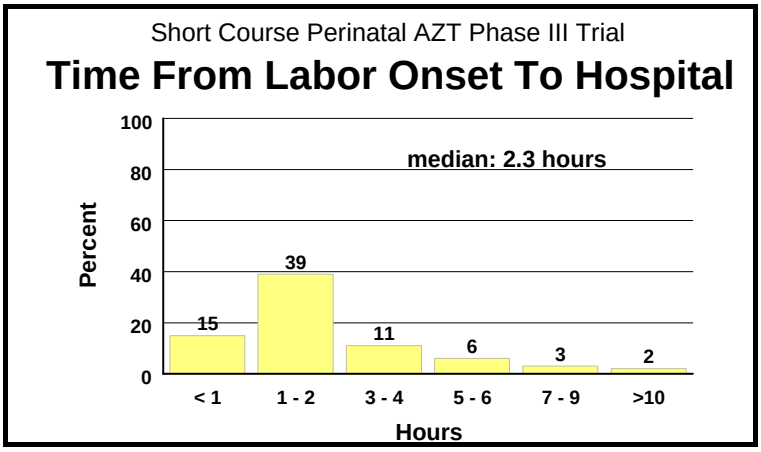


I will now show some of the characteristics of the women. There was no entry criterion in terms of CD4 count, and about 12 percent of the women had CD4 counts less than 200 at enrollment.

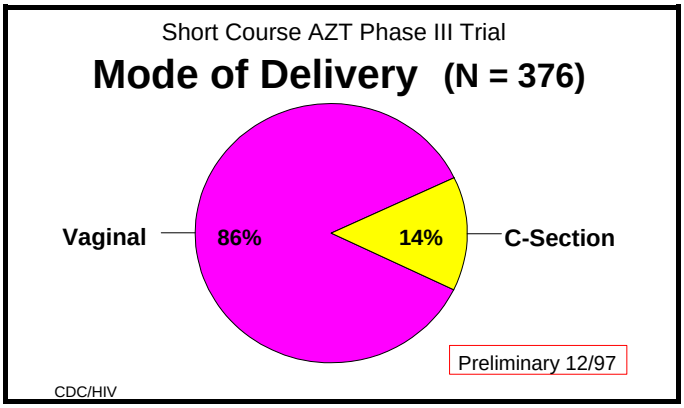


This slide shows the median time on study drug, which was 24 days. Remember, the hospital doctors in the study were estimating the gestational age of the women. This is going to be one of the big challenges for the implementation of a study in a variety of settings–how can you estimate 36 weeks gestation to allow the women to receive enough of the antenatal treatment.

Even with very good estimates of gestational age, we had a bell-shaped curve with a normal distribution in terms of the time women were on antenatal drug. As you can see, about 15 percent of the women had less than 2 weeks of the study drug before the time of delivery. The average time was about 3½ weeks for the antenatal component of drug.



When labor started, women were told to take a labor dose and then to come to the hospital as soon as possible. Again, in our study population, women were very well informed about this, and the women came to the hospital within about 2 hours of the time they recognized the onset of labor. This also will be a challenge in the real world of implementation of the regimen: how are women going to recognize the onset of labor and get to the hospital to continue the intrapartum dosing in-hospital?



This slide shows that we had about a 14 percent caesarean section rate, which was constant during the study. This rate was similar to what we observed before and to the overall rate at these hospitals for the general population.

Baseline Characteristics of Enrolled Women

	ZDV	Placebo
Total women enrolled	198	199
Percent		
Signs/symptoms HIV	13%	12%
C-Section	16%	11%
Median		
Age (yrs)	24	24
CD4+ cells	428	410
Duration labor (hrs)	8.2	9.5
Duration ROM (hrs)	1.8	1.9
Gest. age (wks)	40	40
Birth weight (gm)	3050	2950

This slide shows data that some of you have seen, either in the March 6 *Morbidity and Mortality Weekly Report (MMWR)* or the technical report of the study. The slide compares the ZDV and placebo group in terms of the balance of some of the key characteristics. About 12 percent of the women had some signs or symptoms of HIV. There was a slight difference in the caesarean section rate in the ZDV group, 16 percent versus 11 percent in the placebo group, but this was not significantly different. Women had a mean age of 24 years. The median CD4 count was about 415 for the two groups.

The total estimated duration of labor was about 8 or 9 hours. The median duration of ruptured membranes was about 2 hours. This was quite short, which was interesting. The gestational age overall was about 40 weeks, and the birth weight was about 3,000 grams and was reasonably balanced between the two groups.

Bangkok Short Course Perinatal ZDV Trial

Outcome (5/98) : K-M Analysis

Study Arm	Transmission Rate*
ZDV (n=194)	9.4% (5.3% -13.6%)
Placebo (n=198)	18.9% (13.4% - 24.4%)

P = 0.006

Efficacy --> 50.1% (15.4 - 70.6)

* Kaplan-Meier estimates, based on positive PCR

Let us now look at our final outcome data for efficacy. You saw from the *MMWR* preliminary data that we estimated a 51 percent efficacy. We have now followed all of the children past 2 months in terms of DNA PCR testing, and believe that these are going to be the definitive outcome data. This is based on Kaplan-Meier analysis. This slide shows the new data, indicating that in the placebo group we have an estimated 18.9 percent transmission and in the ZDV group we have 9.4 percent transmission. So the overall the efficacy is about 50.1 percent, based on the Kaplan-Meier analysis, and this is statistically very significant at $p<0.01$. This is basically the same result we announced in February.

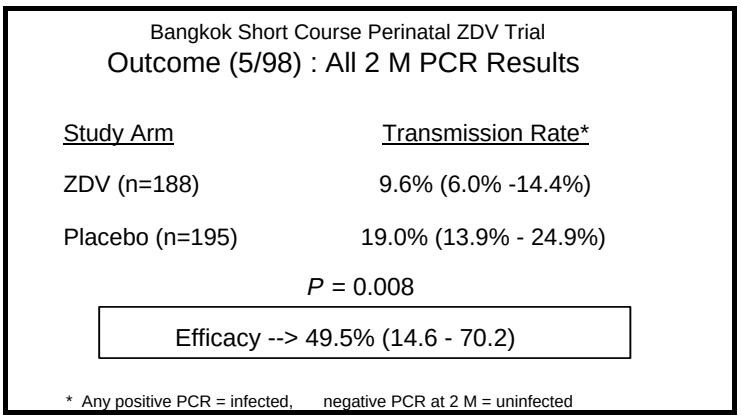
Infant PCR Results (5/98)

	ZDV	Placebo
	Number	
Infants with any PCR results	194	198
Infants with pos PCR	18	37
pos at birth	9	13
neg at birth, pos at 2 m	9	24
neg at 2 m, pos at 6 m	0	0
Infants with neg PCR	176	161
last neg at birth	6	3
last neg at 2 m	28	26
neg at 6 m	138	125

Looking at the PCR results in more detail, we see they are quite interesting. We have a total of 55 children who tested positive by PCR one or more times and are considered infected: 18 in the ZDV group and 37 in the placebo group. If we break this down by whether the PCR was positive at birth, or negative at birth and positive at 2 months, we find that about half of the children in the ZDV group were positive at birth

and about a third were positive at birth in the placebo group. As you can see, 9 of the infected children in the ZDV group were negative at birth and positive at 2 months, and 24 in the placebo group were negative at birth and positive at 2 months. Again, we have had no children who were negative at 2 months and positive at 6 months, and all of the 6-month samples have been systematically tested.

We are almost through with the 6-month follow-up, and we now have about 130 children in each group who have had their 6-month test. In terms of children who last tested negative at 2 months, we have only about 50 children who still need testing before we have full 6-month results on all of the children.



The point of this slide is to emphasize that we were able to make a definitive diagnosis by 2 months in terms of PCR; we did not detect any infections after 2 months and do not expect any new infections among children with the small amount of testing that remains.

We performed an alternate analysis to make sure we were not over-estimating our result by Kaplan-Meier. There is a bit of a gray zone regarding children who are negative at birth. We had about 15 children who did not come back for the 2-month PCR testing. In the Kaplan-Meier analysis, they are considered to be negative. For this alternative analysis, we dropped those children and required that, for children to be considered negative, they had to have a negative PCR result at 2 months. However, we still considered any child with a positive PCR to be infected. Based on this alternate way of calculating efficacy, which is a little bit more conservative, we come out at 49.5 percent, basically the same result.

Transmission Rates,* by Treatment Arm

	N	ZDV	Placebo	All
Overall	383	9.6%	19.0%	14.4%
CD4 count				
< 200	41	23.5%	37.5%	31.7%
200 - 499	209	9.5%	18.3%	13.9%
≥ 500	132	6.2%	13.4%#	9.9%#
Vaginal delivery	327	9.6%	19.3%	14.7%
C-section	56	9.4%	16.7%	12.5%

* Requires ≥ 2 M PCR-negative to be considered uninfected
# p < 0.05

Now I will present some of the data from our stratified analysis, looking at some of the risk factors for transmission and comparing by ZDV and placebo. First, we will look at CD4 count. If you look at the CD4 count within the placebo group, our data show that having a low CD4 count is a risk factor for transmission–transmission decreases from 37 percent to 18 percent to 13 percent with increasing CD4 count.

We see a similar trend within the ZDV group. And it looks like, within each CD4 group, from placebo to ZDV there is some evidence of effectiveness. Although we do not have statistical power for some of these subanalyses, these results are very similar to the data from the 076 study and suggest that ZDV can be effective regardless of CD4 count.

When we compare vaginal delivery with delivery via caesarean section, our data suggest there is some effect on transmission rates when we go from placebo to ZDV in both groups–declining from about 16.7 percent to 9.4 percent in the caesarean section group, and from 19 percent to 9.6 percent in the vaginal delivery group.

Transmission Rates,*by Treatment Arm

	N	ZDV	Placebo	All
Overall	383	9.6%	19.0%	14.4%
≤ 2 weeks Rx	62	3.7%	20.0%	12.9%
> 2 weeks Rx	321	10.6%	18.8%	14.6%
≤ 3 labor doses	216	8.2%	21.5%	14.8%
> 3 labor doses	167	11.4%	15.9%	13.8%
ROM ≤4 hours	272	9.2%	18.3%	14.0%
ROM >4 hours	108	10.7%	21.2%	15.7%

* Requires ≥ 2 M PCR-negative to be considered uninfected
Note: differences not significant

One of the most difficult questions to answer is going to be how much therapy is enough, or is 1 or 2 weeks of therapy going to be enough to reduce transmission risk? We will not be able to have a definite answer to this from our study. But it is interesting that, if you look at placebo compared with ZDV, you do not see a definite dose-response effect related to duration of therapy, and that women who had less than 14 days of the antenatal component had a drop in transmission from 20 percent to about 4 percent. There actually was less of a decrease among women who had more than 2 weeks of therapy. We are still looking at these data, controlling for various factors such as viral load and post-term complications of pregnancy. But we may not be able to come to a definite conclusion about optimal duration of therapy. Our subanalyses do suggest, however, that for women coming in after 36 weeks gestation, it still will be worthwhile to give as much treatment as possible.

We also do not see a clear dose response for number of labor doses. If we look at less than or greater than three labor doses, we see equivalent effects or even more effectiveness, declining from about 21 percent to 8 percent for women who received up to three doses of ZDV intrapartum compared with women who had more than three doses during labor. If there really is decreased effectiveness for women with more than three doses during labor, this might be a marker for women who had prolonged and complicated labors or had other risk factors for transmission. If we analyze duration of ruptured membranes as less than 4 hours and greater than 4 hours, we also see similar effectiveness of the ZDV intervention.

The timing of transmission gets to the issue of the mechanism, or how is the intervention working, and do we need to look at the so-called in utero transmission and intrapartum transmission as different entities. I think some of our preliminary data suggest that most of the effectiveness of the regimen appears to be intrapartum, and this is consistent with our hypothesis going into the study, that most perinatal HIV transmission occurs intrapartum and that the short-course treatment probably would be most effective intrapartum.

To analyze this, we used a fairly standard definition in terms of PCR-positive or PCR-negative results at birth. We used a cut-off of PCR results within 72 hours because basically all of our birth venous blood samples were collected within 72 hours. If we limit this to 48 hours, a more stringent definition, we get basically the same results, but with a little less power.

Efficacy by "Timing" of Transmission

	Inf	N	% Trans	P	Efficacy
In utero					
ZDV	9	188	4.8%	0.42	28.6%
Placebo	13	94	6.7%		
Intrapartum					
ZDV	9	173	5.2%	0.008	61.4%
Placebo	24	178	13.5%		

	N	In utero	Intrapartum
ZDV	18	9 (50%)	9 (50%)
Placebo	37	13 (35%)	24 (65%)

* Kaplan-Meier, based on birth PCR result ≤ 72 hours

What this slide suggests–and this is still preliminary–is that for in utero infection, that is, for children who were PCR positive at birth, there was a 6.7 percent absolute transmission rate in utero, compared with a 4.8 percent transmission rate for the ZDV group. In contrast, we see a big effect in the intrapartum group where for the placebo group we had a 13.5 percent absolute transmission rate compared with 5 percent transmission intrapartum. This difference was highly significant.

So we think there is a big difference in terms of how the short-course regimen is working with respect to timing of transmission, and our conclusion from this is that we are seeing a greater effect in blocking intrapartum transmission. However, we would need to have a larger study and greater power to decide whether the reduction of in utero transmission is significant.

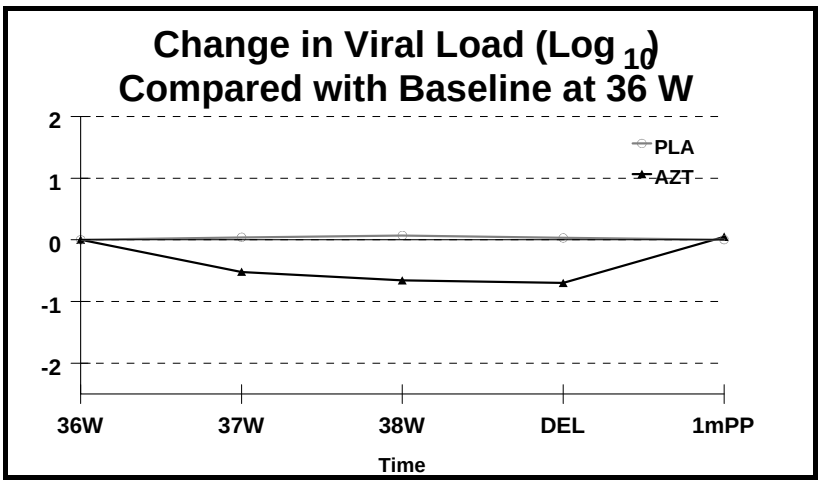
I would like to present to you some of our new data on viral load which we think are very exciting and help explain why the short-course ZDV treatment is working. Let me walk you through a couple of slides on viral load that we will be presenting at the Geneva AIDS conference next month.

Transmission Rates, by Treatment Arm

	N	ZDV	Placebo	All
Overall	383	9.6%	19.0%	14.4%
Enrollment Viral load (RNA copies/ml)				
≤ median	193	2.0%	5.4%	3.6%
> median	190	18.2%	31.4%	25.3%
Log 10				
< 4.0	95	4.0%	4.4%	4.2%
4.0 - 4.5	104	0.0%	7.8%	3.9%
4.5 - 5.0	102	13.5%	26.0%	19.6%
> 5.0	82	27.3%	36.7%	32.9%

When we look at viral RNA copies for the mother at enrollment at 36 weeks and the median value in the groups, for women who had less than the median, the transmission risk was low in the placebo group–5 percent compared with 2 percent in the ZDV group. Although we see some effect, women in the placebo group who had relatively low viral load were at low risk of transmission.

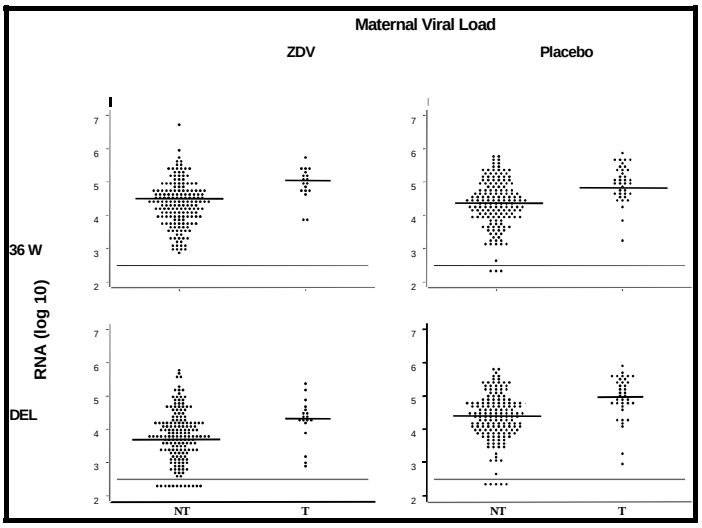
In contrast, women with above the median value viral load at baseline had a very high risk of transmission in the placebo group–31 percent. We basically were able to cut this almost in half using the short-course regimen.



We have conducted a subanalysis of about 75 mothers, about half of whom are on AZT and half on placebo, to look week by week at the change in viral load that was obtained with the short-course regimen. On this slide, the y-axis is in the log scale, and the slide shows the log change in viral load compared with the baseline at 36 weeks. What this shows is that the short-course ZDV treatment produced a rapid effect. By 37 weeks, we already see about a 0.3 or 0.4 log reduction in viral load. By 38 weeks, we saw a 0.5 log reduction in mothers, which stayed constant through delivery.

This may partly explain why we appeared to have effectiveness in women who received less than 2 weeks of drug treatment. If the mechanism is based primarily on decreasing viral load, it produces a decrease in viral load relatively early, which is sustained.

We also measured viral load at 1 month postpartum. Our delivery sample was actually 1 to 2 days after delivery. We did not see a rebound in viral load, which has been suggested as a potential concern particularly in the breast-feeding population, when women stop the antiretroviral short-course treatments.



We now have complete data on viral load at 36 weeks and delivery on the full sample of the study. This is shown in the above slide on the log scale, with the ZDV group at 36 weeks and delivery and the placebo group at 36 weeks and delivery. If I lined up the slide the other way, you would see that the two groups are basically identical at 36 weeks. We have very similar distributions here.

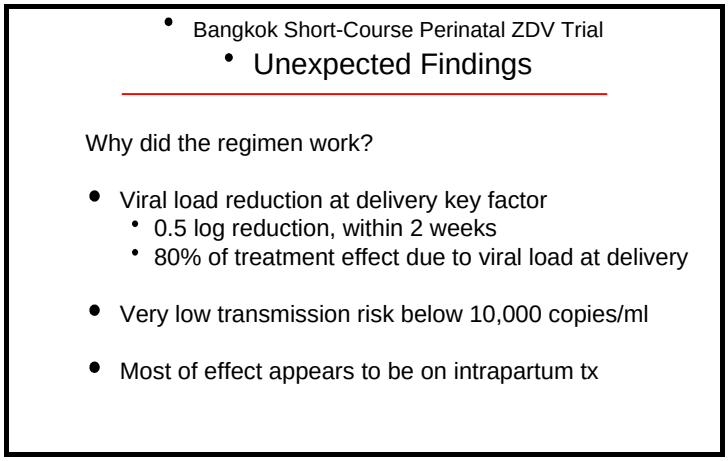
What this slide is showing is that for the full group, from 36 weeks to delivery, we are moving many of the women on ZDV to a much lower level of viral load as we move from 36 weeks to delivery; however, among the placebo group, there is no change from 36 weeks to delivery. I think that this group of women, who we are moving down from their baseline viral load to less than 10,000 copies of viral load, really hold the key to the effectiveness of the regimen. In the ZDV arm, we actually move about 60 women, or one-third of the group, to having less than 10,000 copies RNA.

- Bangkok Short-Course Perinatal ZDV Trial
- Conclusions

Regimen Safe and Effective

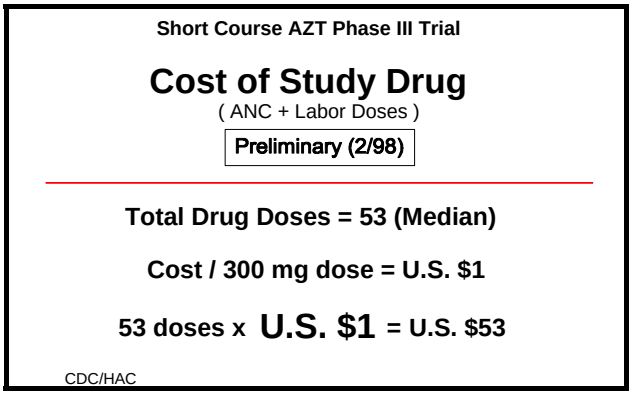
- Short course twice daily oral ZDV, 300mg, starting at 36 wks
  - Safe
  - Well-tolerated
  - Can reduce perinatal transmission by ~50%
- This regimen may be useful for preventing HIV infection in developing countries, where ACTG 076 regimen can not be implemented

In conclusion, we found that the short-course daily dosing of ZDV 300 mg starting at 36 weeks was safe. We will present detailed data on this in other talks. The short-course regimen was very well tolerated, and it can reduce perinatal transmission by about 50 percent. This regimen can be useful for preventing HIV infection in developing countries where the 076 regimen cannot be implemented.

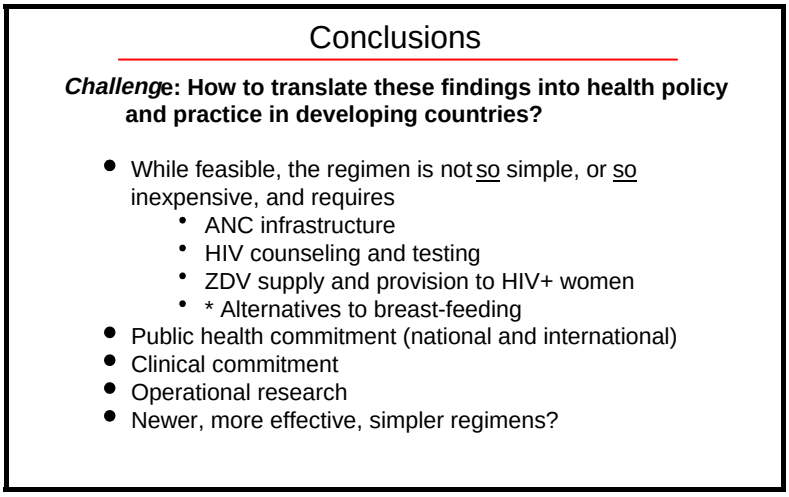


Why did the regimen work? We have seen some preliminary data suggesting that viral load really is the key factor. We saw a 0.5 log reduction in viral load at delivery, which is obtainable within 2 weeks of drug administration, and we think that this holds the key to reducing intrapartum transmission. With some logistic regression modeling that we are now doing, we are estimating that about 80 percent of the treatment effect actually was due to viral load at delivery. This was unexpected, because in the 076 study there was a 0.24 log reduction between entry and delivery, and investigators estimated about a 17 percent treatment effect due to reduced viral load. So the results of 076 suggested that there was something other than viral load that was key. I think that our results suggest that viral load really was much more important.

For women with less than 10,000 RNA copies, transmission risk was very low. And most of the effect, in terms of reduced transmission, was on intrapartum transmission.



I have not mentioned drug cost. Overall, the women got about 53 doses of drug: about 3 doses intrapartum, and about 50 doses antenatally. We have figured the cost of the short-course drug treatment based on the cost of ZDV that was available to the Ministry of Health in Thailand at the start of our study–thus, we estimate about $50 for the short-course treatment. Cost, obviously, may be highly variable. There are many factors that affect cost; hopefully this will change, and the cost of the drug can be reduced further.



In conclusion, the challenge and the purpose of this meeting is how to translate these findings into health policy and practice in developing countries. I would like to end with a cautionary note that, while this regimen is feasible and we are working with our colleagues in Thailand to implement this at the study hospitals and working with the Ministry on several demonstration projects to implement this short course, the regimen is still not so simple or inexpensive. As was already said, the short-course regimen requires an antenatal care infrastructure, HIV counseling and testing, and a ZDV supply for HIV-positive women. Also, one of the key issues will be alternatives to breast-feeding, because this study was done without breast-feeding and we do not know what will happen when the short-course regimen is used with breast-feeding.

There clearly needs to be a public health commitment on the national and international levels to support short-course ZDV for HIV-positive women, and a local clinical commitment by the medical staff at the hospitals.

As I mentioned, we are now moving ahead with our project to look at some of the operational research issues specific to Thailand. At the same time, we are thinking about potential new regimens that will be simpler and more effective. But we are convinced that, based on the results of this study, a strong effort should be made to implement the short-course treatment and to see if we can achieve similar efficacy in the real world situation.